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EXAMINER: B

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days, whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-15 is/are pending in the application.

Of the above, claim(s) 15 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-15 ~~are~~ were subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Notice to Comply

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

★ U.S. GPO: 1996-410-238/40050

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-14, drawn to VEGF antagonists, methods of making and compositions containing said VEGF antagonists, classified in at least class 530, subclass 399, for example.

   II. Claim 15, drawn to a method of treatment, classified in class 514, subclass 12, for example.

2. The inventions are distinct, each from the other because of the following reasons: Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the VEGF antagonists of Group I could be used in a method of generating antibodies rather than in the method of treatment of Group II.

3. Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification, and the search required for Group II is not required for Group I, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Mark Kresnick for Walter Dreger on June 25, 1997 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-14. Affirmation of this election must be made by applicant in responding to this Office action. Claim 15 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Sequence Compliance

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/Or Amino Acid Sequence Disclosures. For example, Figures 1A and 1B, page 48, lines 1-5, and page 53, Table 1 contain nucleotide and amino acid sequences for which there is no listing present in the instant application. Correction is required (see attached Notice to Comply for information on what is required for compliance).

Specification

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claimed invention includes recombinant methods of production and should be included in the title so that it more clearly reflects the claimed invention.

Claim Rejections - 35 USC § 112

8. Claim 1 (and dependent claims 2-14) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VEGF antagonists comprising mutation of cysteine residues of the native VEGF protein, does not reasonably provide enablement for functional derivatives of VEGF antagonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification defines a functional derivative of a polypeptide as "a compound having a qualitative biological activity, or lack thereof, in common with another polypeptide". The breadth of this definition includes any compound (organic, protein, nucleic acid, etc.) which has a biological activity in common with the defined polypeptide, in this case, VEGF. The M.P.E.P. at 2164.08(a) defined this sort of claim as a "Single Means Claim":

> A single means claim, i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. *In re Hyatt*, 708 F.2d 712, 218

> USPQ 195 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.). When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

The instant claims encompass a single means claim because of the language "functional derivatives" and definition of this term in the instant specification (at page 10, beginning line 22). The instant specification is not enabled for any other forms of VEGF other than the native VEGF which has been modified at the cysteine residues because it does not describe the production of any VEGF antagonist ***lacking*** the amino acid sequence of native VEGF.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

By following the guidance presented in the instant specification and sound scientific principles, a practitioner can **not** produce an VEGF lacking the amino acid sequence of Figures 1A-1B, except for the modification of cysteine residues and predict the functional properties of that protein.

9. Claim 1 (and dependent claims 2-14) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "a VEGF antagonist molecule" which is unclear and indefinite because of the use of the abbreviation "VEGF". Because abbreviations can mean various things in the art (i.e. GFR can mean glomerular filtration rate and/or growth factor receptor), the claim should include the full name for which the abbreviation stands. Therefore, the insertion of "vascular endothelial cell growth factor" into the claim would obviate this ground of rejection.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-2, 10-13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Claffey et al. (Biochim. Biophys. Acta. 1246(1): 1-9, 1995).

Claffey et al. teach the mutation of cysteine residues in murine vascular endothelial growth factor (VEGF) to serine residues at various locations in the VEGF molecule (see Figure 3). The mutation of VEGF was accomplished recombinantly, therefore Claffey et al. teach the DNA, vectors and host cells necessary for producing the VEGF mutants (see Materials and Methods at page 2). Claffey et al. teach that some of these variants did not significantly stimulate vascular permeability activity when compared to the wild-type VEGF (see Figure 7). Claffey et al. do not show receptor binding ability, but since some of the VEGF mutants appear to have some stimulatory activity (see Figure 7), the skilled artisan would reasonably expect these mutants to also bind the VEGF receptor, making the VEGF mutants of Claffey antagonists, absent clear and convincing evidence to the contrary. Claffey et al. also teach a composition of VEGF mutants with a pharmaceutically acceptable carrier in that administration of the VEGF mutants for the vascular permeability activity assay would require the proteins in an acceptable carrier. Therefore, Claffey et al. anticipate the instant claims.

12. Claims 1-3, 10-12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Potgens et al. (J. Biol. Chem. 269(52): 32879-32885, 1994).

Potgens et al. teach the mutational analysis of VEGF wherein one of the 8 cysteines of VEGF are mutated to another amino acid (serine). These cysteine residues are numbered in Potgens as 2-5 (only cysteine residues 2-5 were modified) and correspond to amino acid positions 51, 57, 60 and 61 of human VEGF (see Figure 1, page 32880 as compared to Figure 1A of the

instant application). Potgens et al. teach the recombinant production of the VEGF mutants (see page 32880 under Experimental Procedures), including vectors and host cells. These VEGF mutants were all impaired in their ability to form dimers (see page 32881, column 2, paragraph 2). Figure 8 (page 32883) demonstrates the ability of the VEGF mutants to bind the VEGF receptor and Figures 5-7 demonstrate the decreased activity of the VEGF mutants (specifically C2 and C4) compared to the wild type VEGF. Potgens et al. also teach a composition of VEGF mutants with a pharmaceutically acceptable carrier in that administration of the VEGF mutants for bioactivity assays would require the proteins in an acceptable carrier. Therefore, Potgens et al. anticipate the instant claims, absent clear and convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Potgens et al. as applied to claims 1-3, 10-12, and 14 above.

The disclosure of Potgens et al. is described above. Potgens et al. do not teach the recombinant production of VEGF mutants in Chinese hamster ovary cells.

It would have been obvious to one of ordinary skill in the art to create the VEGF mutants of Potgens et al. and to use Chinese hamster ovary cells instead of *E. coli* as the host because use of various hosts for recombinant expression of mammalian proteins is old and well-known in the art. One would be motivated to use Chinese hamster ovary cells instead of the *E. coli* used by Potgens et al. because it would ensure correct glycosylation of the VEGF and because one would have a reasonable expectation of success in using Chinese hamster ovary cells as a host for production of mutant VEGF because these cells are commonly used in the art at the time the invention was made. Therefore, the instant invention would have been *prima facie* obvious, absent clear and convincing evidence to the contrary.

15. Claims 4-6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potgens et al. as applied to claims 1-3, 10-12, and 14 above.

The disclosure of Potgens et al. is described above. Potgens et al. do not teach the use of aspartic acid for the substitution of cysteine, the combined substitution of cysteine at amino acid positions 51 and 60, or "further amino acid modifications that do not otherwise affect the essential biological characteristics".

Potgens et al. clearly teach the substitution of cysteine residues in VEGF, specifically at amino acid positions 51 and 60, in order to prevent dimerization of the VEGF monomers. Dimerization is necessary for receptor activation by VEGF (see page 32880, column 1, paragraph 1). Therefore, it would have been obvious to one of ordinary skill in the art at the time the

invention was made to substitute the cysteine residues of VEGF which are necessary for dimerization with another amino acid in order to prevent the disulfide bond formation which occurs between the cysteine residues and results in dimerization. Potgens et al. substitute the cysteine residues with serine, however, substitution of cysteine residues with any amino acid would serve to prevent the disulfide bond formation from occurring (and therefore, dimerization). The substitution of cysteine residues with aspartic acid would also be obvious to the skilled artisan because there is a reasonable expectation of success in obtaining a monomeric VEGF similar to that of Potgens et al. because aspartic acid has the same backbone structure as cysteine and serine. The skilled artisan would reasonably expect the monomeric VEGF which has aspartic acid substituted for cysteine to retain the receptor binding ability of the serine substituted mutants of Potgens et al. because the protein would be expected to fold in a manner similar to the native monomer or serine substituted mutant and would therefore be useful as antagonists, absent clear and convincing evidence to the contrary.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cysteine residues of VEGF at both positions 51 and 60, making a double mutant, because Potgens et al. teach that these two amino acid positions are important in dimerization and that single mutations in these positions still resulted in a minor amount of dimerization (negligible with amino acid position 51 and 20% with amino acid position 60; see page 32881, column 2, paragraph 2). The skilled artisan would be motivated to create the double mutant wherein the cysteine residues of amino acid positions 51 and 60 are substituted

with another amino acid because Potgens et al. teach that these two positions are important in dimerization of VEGF (see page 32880, column 1, paragraph 1), and the mutation of these two position would prevent dimerization and create a VEGF antagonist, absent clear and convincing evidence to the contrary.

Claim 9 is directed to "further amino acid modifications that do not otherwise affect the essential biological characteristics". At the time the invention was made, it was well within the skill of the artisan to make amino acid modifications which do not result in any substantial alteration in biological activity. For example, the substitution of arginine for lysine is considered a conservative amino acid substitution and would be expected to alter the biological activity of a protein. Frequently, amino acids are altered in order to create cleavage sites or glycosylation sites. Therefore, because it was well known in the art at the time the invention was made to generate amino acid alterations within a protein which do not affect the biological activity of the protein, it would have been obvious to one of ordinary skill in the art to modify the VEGF mutants of Potgens et al. by further modifying the amino acids of VEGF in such a way that the biological activity is not affected, absent clear and convincing evidence to the contrary.

Therefore the invention as a whole would have been *prima facie* obvious at the time it was made.

16. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potgens et al. as applied to claims 1-3, 10-12, and 14 above in view of Pang (U.S. Pat. No. 5,418,135).

The disclosure of Potgens et al. is described above. Potgens et al. do not disclose the chemical modification of cysteine residues.

Pang teach the elimination of disulfide bonding of PDGF in order to prevent dimerization of the PDGF (see column 3, lines 35-38). This is accomplished by the elimination of the cysteine residues or by blocking the cysteine residues chemically (see column 3, lines 39-40 and 45-48; column 11, lines 17-29). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the chemical modification of cysteine residues as taught by Pang to modify the cysteine residues of VEGF as taught by Potgens in order to prevent disulfide bond formation between the cysteine residues which are responsible for dimerization in order to create a VEGF antagonist. The skilled artisan would have a reasonable expectation of success in obtaining a VEGF monomer because Potgens et al. teach that the disulfide bond formation is necessary for dimerization and Pang teach that chemical modification of cysteine residues prevent disulfide bond formation. Furthermore, the of protein (PDGF) of Pang is structurally and functionally similar to VEGF, and the skilled artisan would reasonably expect that a chemical modification which was tolerated in PDGF to be tolerated in VEGF, absent clear and convincing evidence to the contrary.

Conclusion

17. No claim is allowed.

18. In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents **must** be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116, which will be strictly enforced.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Thursday from 8AM to 4PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
June 30, 1997

JOHN ULM
PRIMARY EXAMINER
GROUP 1800